Medicine Cabinet

The glitazones: proceed with caution

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INTRODUCTION

Type 2 diabetes mellitus is characterized by the early onset of insulin resistance. Reduced responsiveness to normal circulating levels of insulin leads to hyperinsulinemia. When the pancreas is unable to keep up with increased insulin requirements, hyperglycemia ensues. This can influence the development of diabetes mellitus, obesity, hypertension, and dyslipidemia.[1-3] Commonly referred to as "syndrome X," these complications are associated with an increased risk of coronary heart disease.

A new class of drugs, the glitazones, offers the first therapeutic option specifically targeting insulin resistance. The drugs act on tissues such as liver and skeletal muscle, sensitizing them to insulin action, and thereby increasing glucose uptake and decreasing its hepatic output.

Summary points

- The glitazones are indicated for the treatment of type 2 diabetes
- Clinical research has unveiled a unique mechanism of action and appreciable efficacy for these drugs
- Despite promising preclinical data, case reports of liver toxicity, weight gain, and edema have been published
- Troglitazone has been removed from the market by the Food and Drug Administration because of concerns about its safety
- The poor safety record and high costs of glitazones preclude their use as monotherapy
- Glitazone use has a role, in combination with insulin, sulfonylurea, or metformin
- Patient benefits can be achieved through careful and appropriate prescribing and monitoring practices

THE GLITAZONES

Troglitazone

The oldest and best studied of the glitazones is troglitazone. Clinical trials in the past have examined its use either as monotherapy or as treatment in combination with metformin, sulfonylureas, or insulin.[4-27] These confirmed its ability to decrease fasting plasma glucose and hemoglobin (Hb) A_{1c} concentrations. The US Food and Drug Administration (FDA), however, withdrew the drug from the market on March 21, 2000, because of concerns about its safety.

Rosiglitazone

Nine clinical trials of rosiglitazone have been carried out.[28-36] Average decreases in Hb A_{1c} concentrations ranged from 0.3% to 1.6%. Two of the clinical trials looked solely at fasting plasma glucose levels, reporting decreases from 15.8 to 45.9 mg/dL (0.9 to 2.6 mmol/L).[33,36]

Monotherapy trials comparing once-daily dosing with twice-daily schedules reported enhanced efficacy with the latter. Optimum dosing schedules have not been studied in combination treatments.

In one study of patients taking insulin, there was a 4.8% to 9.4% decrease in daily insulin requirements when rosiglitazone was added.[35] However, symptoms of hypoglycemia were observed more frequently in patients receiving this combination than in patients receiving insulin alone.[35]

Another study compared the safety of rosiglitazone when used in patients older and younger than 65.[28] Most adverse effects were classified subjectively as mild or moderate, with a similar incidence of each in patients from both age groups. Notably, edema was reported in 3.0% to 4.8% of patients on either single-agent or combination therapy.

Pioglitazone

Six trials studying the efficacy of pioglitazone for use in diabetes have been published in abstract form.[37-42] According to the product labeling, pioglitazone decreases Hb A_{1c} levels compared with placebo by an average of 1.0% to 1.6% when used as monotherapy and 0.7% to 1.3% when used in combination regimens. Although the manufacturer promotes pioglitazone as having a positive effect on serum lipid profiles, clinicians should be aware that at least some of the patients studied were simultaneously taking β-hydroxy-β-methylglutaryl-CoA reductase inhibitors. Thus, it is not possible to comment on the true effects of pioglitazone on serum lipids.

EFFICACY AND SAFETY

Despite subtle differences between rosiglitazone and pioglitazone, a review of the literature reveals that they differ little in efficacy. Analysis of the pooled trial data shows that the 2 agents still on the market are more effective than placebo in reducing fasting plasma glucose and Hb A_{1c} concentrations, and the response rates are correlated with daily dosages.

Prevailing clinical wisdom suggests that glitazone therapy should be initiated with full therapeutic doses and that therapy should be discontinued if no clinical improvement occurs within 8 to 12 weeks. The need for prompt discontinuation in patients receiving marginal or no benefit is driven by evidence of 3 serious toxic effects associated with these agents: hepatotoxicity, edema, and

Table 1 *Comparison of FDA-approved indications and dosing recommendations for the 2 approved glitazones*

Drug	Rosiglitazone	Pioglitazone
HMC/UWMC drug formulary status	Formulary	Nonformulary
Date of FDA approval	5/25/99	7/15/99
FDA-approved indications	Monotherapy; combination with metformin	Monotherapy; combination with insulin; combination with sulfonylurea; combination with metformin
Tablet sizes, mg	2, 4, 8	15, 30, 45
Manufacturer recommended dose	Combination: 2 mg bid, 4 mg daily to bid, 8 mg daily	Combination: 15-30 mg daily
Contraindication	ALT > 2.5 × ULN	ALT > 2.5 × ULN
ALT monitoring frequency	ALT at baseline, every 2 mo for 1 yr, then periodically	ALT at baseline, every 2 mo for 1 yr, then periodically

FDA = Food and Drug Administration; HMC = Harborview Medical Center/Unversity of Washington Medical Center; bid = twice daily; ALT = alanine aminotransferase; ULN = upper limit of normal.

weight gain. Evolving reports of these adverse effects have led to a sharp decline in glitazone use.

Hepatotoxicity

At least 43 cases of acute hepatic failure have been reported in patients taking troglitazone after the FDA initially approved its use in 1997. Of these, 28 deaths occurred.[43-49]

The association between liver toxicity and the 2 other glitazones is less clear. Analysis of 3,455 patients treated with rosiglitazone in double-blind, placebo- or active-controlled trials showed no evidence of hepatotoxicity.[50] However, 2 cases of hepatotoxicity following rosiglitazone use have been reported.[51,52] At this time, no reports of liver damage linked to pioglitazone have been published. Strict adherence to guidelines for monitoring liver aminotransferase levels in patients treated with glitazones is the cornerstone of their safe prescribing (table 1).

Edema and weight gain

In addition to sporadic reports of hepatotoxicity, other phenomena such as fluid retention, blood plasma volume expansion, and edema appear to be a glitazone class effect. According to current manufacturer recommendations, the drugs are not indicated for patients with New York Heart Association class 3 or 4 status, unless the benefits of therapy are expected to outweigh the risks. Two cases of troglitazone-induced edema have been reported.[53] One patient developed lower extremity edema after 8 months of therapy. Troglitazone was discontinued, and the patient subsequently lost 7.1 kg (16 lb) within 3 weeks. The second patient presented with orthopnea and edema at 9 months, and following drug discontinuation 12 months later, lost 9.1 kg (20 lb) over 3 weeks.

Clinical observations at the University of Washington/Harborview Medical Center, Seattle, suggest that patients with preexisting edema may experience symptom exacerbation on initiation of glitazone therapy. It is important for physicians to monitor these patients and to record body weights frequently as a means of detecting possible fluid overload and the onset or worsening of edema.

Trials report significant weight gain for patients receiving glitazones.[22,27,29,31-33,35] The experience of our Diabetes Care Center, summarized in 2 case reports,[54] indicates that the weight gain from glitazones is greater than that suggested in the product literature. In these 2 patients, fluid retention was a large and substantial component of the weight gain. After fluid status normalized, however, both patients remained above their starting weights 7 and 12 months after troglitazone discontinuation. These drugs may, therefore, cause weight gain through other mechanisms, perhaps involving the stimulation of fat accumulation.[55-57]

SHOULD GLITAZONES BE USED IN MONOTHERAPY?

Rosiglitazone and pioglitazone are approved for use as monotherapy. But their single-agent use is precluded by concerns about safety, the high drug costs (table 2), and the costs of mandatory liver function monitoring. Until these issues are addressed, insulin, metformin, and sulfonylureas remain less expensive and safer alternatives.

Table 2 *Monthly University of Washington Medical Center/Harborview Medical Center outpatient charge for rosiglitazone**

Drug strength and dosing schedule	Patient charge, $
2 mg orally twice daily	71.06
4 mg orally daily	49.01
4 mg orally twice daily	98.03
8 mg orally daily	89.45

*As of May 24, 2000.

CONCLUSION

Despite advances in pharmacotherapy, type 2 diabetes continues to be underdiagnosed and undertreated. By selectively unlocking insulin resistance, glitazones can be used for carefully selected patients to achieve better glycemic control. When properly prescribed and carefully monitored, they can effectively reduce fasting plasma glucose and Hb A_{1c} levels in some patients.

Continued reports of serious adverse effects, however, hinder their widespread use and acceptance. To receive maximum benefit from these drugs, patients require repeated body weight measurements, periodic liver function tests, monitoring of plasma glucose and Hb A_{1c} concentrations, and adherence to follow-up appointments and lifestyle modifications. The unknown potential for long-term morbidity, the relatively high cost of therapy, and reports of hepatotoxicity, edema, and weight gain all argue against monotherapy. Rather, these insulin sensitizers are more appropriately considered complementary to other oral antidiabetic drugs.

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Netphiles

Exploring the genome

Progress is being rapidly made on the human genome project. It is the power of information processing technology that has made such achievements even thinkable; and that power is also used to allow instantaneous communication of results to a global network of collaborating (and competing) researchers. The starting point for exploring their work is http://www.ncbi.nlm.nih.gov/genome/seq/.

Just contemplating the volume of data that the site has to serve now takes your breath away; when the sequence is complete it will be truly awesome. With such demands it is fitting that the site's design clothes its content in a user interface of beguiling simplicity. On a web choked with gratuitous graphics, this site uses them entirely appropriately. The site is organized by chromosome. Each is linked to a page that describes the current progress with mapping its genes and shows a more detailed graphic of the chromosome. Areas already sequenced are marked with red and orange bands. Click on a band and up come the genes themselves, represented as vertical blue lines. Pick a line, and the gene sequence itself, in all its ggcgtgaatt glory, downloads to your browser. (Tourists should not do this too often: 200 kilobases generates a bandwidth-choking file of more than 200 kilobytes: so look for a short one). If you have a gene sequence to identify, the site's BLAST feature (http://www.ncbi.nlm.nih.gov:80/BLAST/) enables the search to be made in reverse. A comprehensive review of this site's informational features requires a PhD in molecular genetics. Those of us not so endowed might begin with a glossary (http://www.ornl.gov/hgmis/publicat/glossary.html) and a primer in human genetics (http://www.bis.med.jhmi.edu/Dan/DOE/intro.html).

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We welcome suggestions for Web sites to be included in future Netphiles